REMARKS

Status of the Claims

Claims 1-2, 5 and 8, 11, and 20-21 are pending.

Claim 1 has been amended to incorporate claim 21.

Claim 21 has been cancelled.

No new matter has been added.

1. Claim Rejections under 35 USC Section 103

On pages 3-5 of the Office Action, the Examiner rejects claims 1-13 as allegedly obvious over Somerville et al. (W0 03/066039) in view of Wong et al. (USPN 6,964,962) and Saji et al., U.S. Patent 5,532,372). Applicants respectfully traverse.

1.1 The references do not make obvious the claimed dose range.

As a preliminary matter, Applicants note that the Examiner has found it necessary to add an additional reference to the obviousness rejection. The Examiner has already admitted that Sommerville does not disclose a particular dose of SM-13496. (Office Action page 3, lines 10-11). The Examiner also admits that Wong et al. "teach [a] wide range of dosage." (*Id.* at line 17). Consequently, Applicants submit that the Examiner has recognized that the previous obviousness rejection was deficient, at least because it did not disclose the dosage as claimed in the present application.[1]

[1] To ensure the record is complete, Applicants reiterate that Wong, in combination with Sommerville, does not render the present invention obvious because Wong teaches a broad dosing of SM-13496 *in combination* with a norepinephrine reuptake inhibitor, and that the dose range for SM-13496 would either not be effective, or would not be tolerated by a patient. (See Amendment dated June 17, 2008, page 7-9).

The Examiner cites Saji for teaching "oral preparations of the claimed compound containing 10 mg, 20 mg, or 40 mg of a hydrochloride of formula 1." (Office Action, page 3). The Examiner further argues, "when the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in the range or value is minor." *In re Geisler*, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997), *quoting Haynes Int'l, Inc. v. Jessop Steel Co.,* 28 USPQ2d 1652, 1655 n.3 (Fed. Cir. 1993).

Applicants submit that Saji does not remedy the deficiencies of the combination of Wong and Sommerville to establish *prima facie* obviousness because the difference between the range is not minor. Saji discloses an *extremely* broad range of compounds (almost 200 compounds), which it claims have "significant" anti-psychotic activity (See col. 12, lines 25-28; and col. 2 lines 9-15 and 64-65). In contrast to the Examiner's assertions, Saji discloses that *any one* of this broad range of compounds could be administered in "a dose of from about 1 to 1,000 mg, preferably from about 5 to 100 mg, in case of oral administration and at a daily dose of from about 0.1 to 1000 mg, preferably from about 0.3 to 50 mg, in case of intravenous injection." (Saji, col. 12, lines 19-23). Furthermore, the *in vivo* methods disclosed in Saji merely disclose "a designated amount of the test compound is orally administered." (Saji, col. 13, lines 30-31). Thus, Applicants submit that one of skill would not be able to determine which particular compound would be effective at any particular dose range from the disclosure in Saji.

Moreover, Applicants submit that the dosage of Saji does not speak to efficacy against the negative symptoms of schizophrenia. Saji is directed to a an "anti-psychotic" drug, which may be effective against "schizophrenia, senile insanity, manic-depressive psychosis, neurosis, etc.." (Saji, col. 1, line10-12). Saji does not disclose that this compound can be used for treatment of the negative symptoms of schizophrenia and/or the cognitive dysfunction of schizophrenia. Moreover, at the time of filing, treatment of the negative symptoms using an atypical neuroleptic for schizophrenia which did not have adverse side effects was not recognized except by the inventors. (See Amendment dated July 16, 2008, page 10).

The *in vivo* data in Saji shows that the compound has an ED_{50} of 10.3 mg/kg in mice in a test directed to the inhibition of the stimulation of dopamine receptors in the striatum. (Saji, col. 13, line 65).

However, Applicants emphasize that the mouse (or rat) anti-climbing activity test is not specifically directed to schizophrenia, nor does it relate to efficacy against the negative symptoms of schizophrenia. See for instance, D. Wang et al., Neuropharmacology, 52 1179-1187 (2007) (attached) which discloses that positive symptoms arise from a subcortical hyperstimulation of dopamine D-2 receptors in striatal areas and negative symptoms are thought to arise from a doopaminergic hypofunction that results in the hypostimulation of dopamine-D1 receptors in dorsolateral prefrontal cortex (PFC) in schizophrenia patients. (Wang et al., page 1179, right column, bottom of the page and page 1180, left column, line 6-8). Furthermore P. Protais et al., Phychopharmacology 50, 1-6 (1976) (attached) teaches that climbing behavior is useful for screening the positive symptoms of schizophrenia induced by dopamine. Specifically, Protais at page 3, table 2 disclosed that various neuroleptics inhibited the apomorphine-induced climbing behavior. Similarly, Protais at page 5, right column, 3 lines from the bottom, states that "this test already appears useful for the screening of neuroleptics, as well as for the study of the dynamics of cerebral dopamine receptors."

Thus, Applicants submit that the teachings of Saji are not relevant to efficacy against the negative symptoms of schizophrenia.

Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants request that the Examiner withdraw the rejection.

1.2 <u>The Instantly Claimed Methods for Treating Schizophrenia Provide Surprisingly Improved Results</u>

1.2 (a) *The Unexpected Lack of Negative Side Effects Provided by the Instantly Claimed Methods for Treating Schizophrenia*

On page 4 of the Office Action, the Examiner attempts to justify the instant obviousness rejection by relying on the *In re Aller* rule that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454,456, 105 USPQ 223, 235 (CCPA 1955).

Applicants submit that any *prima facie* case of obviousness "can be rebutted if the applicant (1) can establish the existence of unexpected properties in the range claimed or (2) can show that the art in any material respect taught away from the claimed invention." *In re Geisler,* 43 USPQ2d at 1365 (internal quotations omitted).

Because, prior to the instant invention, the dogma in the field of schizophrenia therapy was that atypical neuroleptics were ineffective at treating the negative symptoms of schizophrenia and because the instantly claimed schizophrenia treatment provides for the effective treatment of the negative symptoms of schizophrenia, the instantly claimed treatment methods provide surprisingly improved results. Applicants submit that the effect of this compound against the negative symptoms of schizophrenia overcomes any showing of *prima facie* obviousness the Examiner may have presented.

1.2 (b) *The Declaration is effective to compare the prior art to the present invention.*

The Examiner asserts that the Declaration of the study of the maximum tolerated dose of SM-13496 is not sufficient to overcome the rejection based on the prior art since Applicants have not shown comparative analysis of the prior art versus the claimed invention. Applicants respectfully disagree.

The Ogasa Declaration compares the administration of lurasidone as disclosed in Sommerville and Wong to the administration of lurasidone as disclosed in the present invention. Sommerville, which the Examiner describes as the primary reference, does not teach a dose.[2] Therefore, Applicants used

[2] Just because the Declaration does not explicitly state that the Declaration is a comparison of the present invention against Sommerville *and* Wong does not mean that the Declaration does not compare the invention to the teachings of the closest prior art, that is either Sommerville or Wong. Moreover, Applicants wonder how they were supposed

the Declaration to illustrate that lurasidone cannot be administered without some knowledge as to dose range. The Examiner then pointed out that Wong taught administration of lurasidone (in combination with a norepinephrin inhibitor) over a given dose range. The Declaration compares administration of lurasidone over a subset of the range of Wong, and shows that administration of lurasidone according to Sommerville using the dose range of Wong would either be ineffective or not be tolerated due to adverse effects. Therefore, Applicants submit that the Declaration directly compares the teachings of both Sommerville and Wong to the present invention.

The Examiner also indicates that Saji et al. discloses the dose range of the claimed compound, and appears to suggest that Saji is the closest prior art.[3] However, Applicants disagree. As discussed above, the Saji reference does not discuss the negative symptoms of schizophrenia. Moreover, comparing the Saji reference against the Declaration, the Saji reference teaches that adverse side effects have an ED_{50} of at least 747 mg/kg and possibly more than 1000 mg/kg; much higher than either the Maximum Tolerated Dose (400 mg/kg) or the Minimum Intolerable Dose (520 mg/kg) disclosed in the Declaration. (Saji, col. 14, lines 26 and 45 and Declaration page 2, respectively). Applicants therefore submit that the Examiner's dismissal of the Declaration is improper.

For these reasons, and those detailed above, Applicants respectfully request that the Examiner withdraw the obviousness rejection and allow all claims.

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to compare the method of Sommerville alone, which does not teach a dose, to the present invention in any meaningful way, since there was not sufficient information to establish an experimental protocol.

[3] Applicants note that the Saji is *newly cited* prior art. When the Declaration was filed, its experiments compared the methods of the references cited against Applicants, i.e., Sommerville and Wong. However, that does not mean that the Declaration is not relevant to the Saji reference. But that does mean that the Examiner's cursory dismissal of the teachings of the Declaration as lacking "comparative analysis" to Saji is wholly improper.

2. Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Registration No 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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